Effect of continuous venovenous hemodiafiltration on darunavir and raltegravir exposure after administration via a gastroduodenal tube

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Effect of Continuous Venovenous Haemodiafiltration on Serum Darunavir and Raltegravir concentrations after Drug Administration via a Double-Lumen Nasogastroduodenal Tube

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To the Editors:

We present a 43-year-old HIV-positive man (74kg, 178cm) who was admitted with respiratory failure, persistent pulmonary infiltrates, fever, pleural effusion, ascites, thrombocytopenia, diffuse lymphadenopathy, splenomegaly, Kaposi sarcoma and high serum HHV-8 DNA-levels. The antiretroviral treatment-experienced patient had 166 CD4 cells/µl and an HIV-1 viral load of 1.7 Mio copies/ml. Lymph node biopsy confirmed the diagnosis of multicentric Castleman disease. Antiretroviral therapy was commenced with lamivudine, zidovudine, ritonavir boosted darunavir and raltegravir. Intravenous etoposide and valganciclovir were added in accordance with Oksenhendler [1]. Because of subsequent multiorgan failure a period of mechanical ventilation and continuous renal replacement therapy (CRRT) was required. Continuous venovenous haemodiafiltration (CVVHDF) was instituted with a Fresenius Multifiltrate dialysis machine (Fresenius Medical Care, Bad Homburg, Germany) using a high-flux polysulfone capillary haemofilter with a membrane surface area of 1.8m^2 (Ultraflux® AV 1000S). Blood flow rate was 180mL/min, dialysate flow rate was 1500mL/h, pre-dilution substitution flow rate was 1500mL/h and fluid removal rate was 100-200mL/h. Urine production was 5mL/hour, serum creatinine 47µmol/L, serum albumin 19g/L (normal 40–49g/L) and liver enzymes within normal range. Antiretroviral therapy, citalopram, levothyroxine, esomeprazole, ursodeoxycholic acid and folic acid were administered via the gastric port and simultaneous enteral nutrition (Optifibre®) via the duodenal port of a double-lumen nasogastroduodenal tube. Zidovudine (300mg q12h), lamivudine (50mg q24h) and ritonavir (100mg q12h) dosing was in accordance with guidelines for patients undergoing CRRT [2]. No such guidelines exist for darunavir and raltegravir. As no dose-adjustments are necessary for darunavir and raltegravir in renal failure, the usual doses of 600mg and 400mg q12h, respectively, were continued after the institution of CVVHDF.

Nevertheless intermittent haemodialysis was found to decrease post-dialysis darunavir concentrations by 57% and raltegravir concentrations by 82% from their pre-dialysis levels in a case described by Giguère et al [3] suggesting an increased clearance during renal replacement therapy. Similar to Giguère et al, Bernard et al also found significant reductions in raltegravir plasma concentrations after haemodialysis sessions [4], however, others report no reduction [5]. Due to lack of information regarding darunavir and raltegravir dosing in CRRT, the controversial data regarding the effect of haemodialysis on raltegravir concentrations [3-5], the presence of hypoalbuminaemia predisposing to increased drug clearance and the importance of maintaining antiretroviral drugs within therapeutic

range, we determined the clearance of these substances on CVVHDF by pharmacokinetic sampling. We were additionally interested to determine whether drug administration via the gastric port with simultaneous feeding via the duodenal port of the nasogastroduodenal tube affected drug absorption and exposure.

Darunavir and raltegravir pharmacokinetic sampling was performed on day 2 of CVVHDF, 5 days after drug commencement. Peripheral plasma samples were taken pre-dose and 2 and 6 hours post-dose in order to estimate the area under the time-concentration curve ($AUC_{0\text{-}12h}$) which was calculated according to the trapezoidal rule. A rough estimate of total oral clearance (Cl) was determined according to the formula $Cl = F \cdot Dose/AUC_{0\text{-}12h}$, (F = oral bioavailability). In order to determine the sieving coefficient and CVVHDF drug clearance, additional measurement of darunavir and raltegravir concentrations in the filter afferent line, the efferent line and the ultrafiltrate line two hours after drug administration were performed. Concentrations were determined by high-pressure liquid chromatography and a diode array detector. Results and data from previously published pharmacokinetic studies in young, healthy males are shown in the Table.

Both darunavir and raltegravir were removed by CVVHDF with approximately the same clearance as provided by a normally functioning kidney. Absorption of both drugs after suspension and application via the gastric port with continued administration of feed via the duodenal port of the double-lumen tube was good. After administration of a single dose darunavir/ritonavir 400/100mg in 4 fasted healthy volunteers mean time to peak serum concentration (t_{max}) was 0.75 hours and the mean peak concentration (C_{max}) was 5.125 ± 0.906mg/ml [6]. The 2-hour post-dose darunavir concentration in our patient was higher, reflecting the higher dose administered (600mg). Following ten days of multiple-dose raltegravir administration (400mg q12h) in fasted volunteers, t_{max} was 1 hour and C_{max} was 4.96mg/l [7]. In our patient the raltegravir plasma concentration was 2.37mg/L two hours post-dose, which can be explained by sampling at a later time-point. For comparison, the reported HIV-1 IC_{5o} for darunavir is 0.003 – 0.029 µM (0.0016 – 0.016 mg/L) [8] and the reported IC_{5o} for raltegravir is 10nmol/L (0.0055mg/L) [9]. Good antiviral coverage was thereby provided throughout.

We conclude that dose-adjustments are not required for patients receiving darunavir and/or raltegravir whilst undergoing CVVHDF and that absorption of darunavir and raltegravir is not significantly affected by postpyloric enteral feeding.

Table: Pharmacokinetic parameters of darunavir and raltegravir

	Darunavir	**Raltegravir**
Whilst undergoing continuous veno-venous haemodiafiltration:		
Dose (mg) /12h	**600**	**400**
(Q_{uf} + Q_D) (ml/min)	51.7	51.7
Dilution factor (df)	0.878	0.878
C_0 (mg/L)	**4.4**	**0.25**
C_2 (mg/L)	**6.1**	**2.37**
C_6 (mg/L)	**5.7**	**0.47**
$AUC_{0\text{-}12h}$ (mg/mL*min)	7.74	0.66
C_{uf} (mg/L)	**0.7**	**1.06**
C_{pre} (mg/L)	**5.9**	**2.32**
C_{post} (mg/L)	**6.2**	**2.06**
SC	0.116	0.484
Cl_{CVVHDF} (mL/min)	5.2	22.0
Oral Cl_{tot} (mL/min)	78	606
Percentage of total oral clearance due to CVVHD	7%	4%
Published pharmacokinetic parameters:		
Qo (extra renal elimination fraction)	0.923 [12]	0.91 [11]
Total body clearance (intravenous) with ritonavir	100mL/min [12]	
Total oral clearance		600ml/min [13]
Renal clearance	7.7ml/min	60.5ml/min [7]

Figures in bold are measured figures. Other figures are derived using the equations given below and in the text.

AUC = area under the curve, C_0 = plasma drug concentration immediately before dosing, C_2 = plasma drug 2 hours after dosing, C_6 = plasma drug concentration 6 hours after dosing, C_{uf} = ultrafiltrate drug concentration 2 hours after dosing, C_{pre} = drug concentration in plasma taken from the efferent haemodiafilter port (`pre-filter`), C_{post} = drug concentration in plasma taken from the afferent haemodiafilter port (`post-filter`), SC = sieving coefficient, Cl_{CVVHDF} = clearance due to haemodiafiltration, Cl_{tot} = total clearance Q_{uf} = ultrafiltration flow rate, Q_D = dialysate flow rate. To calculate sieving coefficient (SC) and Cl_{CVVHDF} standard formulae were used [14, 15]. Cl_{CVVHDF} = SC x (Q_{uf} + Q_D) x df Sieving coefficient (SC) = 2 X C_{uf} / (C_{pre} + C_{post}). Dilution factor (df) = Q_{BF}/(Q_{BF} + Q_{RF}). Q_{BF} = blood flow rate, Q_{RF} = substitution rate

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